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10/565,322	01/20/2006	Evangelos Karavas	PHARMA-101	2221

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NEWTON, MA 02466

EXAMINER	
RAO, SAVITHA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,322	KARAVAS ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-23 are pending and under consideration in the instant office action.

Election/Restrictions

Applicant's election with traverse of the following species in the response filed on 11/21/2008 is acknowledged.

"Gelling agent": Hydroxypropylmethylcellulose

"Non-swelling polymer": poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, commercially available as Eudragit RS 100,

"Conjugation agent": sodium lauryl sulphate

"Coating polymer": Poly (butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1:2:1 copolymer, commercially available as Eudragit E.

"Water soluble compound": low viscosity hydroxypropylmethyl cellulose

The traversal is on the ground(s) that the subject matter of each group of species are closely related to others, and have either common property or activity or common structure and thereby have unity of invention.

Examiner finds the applicant's argument persuasive and withdraws the specie election requirement set forth in the restriction requirement dated 07/22/2008

Applicant timely traversed the restriction (election) requirement in the reply filed on 1/21/2008. Restriction for examination purposes as indicated is proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 -23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sherman et al (US 6419958) in view of Oosterbaan et al. (US 6696496) further in view of Mulye (US 2002/0155156).

Sherman et al teaches a 24 hour extended release dosage formulation and unit dosage form of venlafaxine hydrochloride, which provides better control of blood plasma levels that conventional tablet formulation which are administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets (abstract). Sherman teaches that extended release capsule dosage form comprising film coated spheroids are placed in pharmaceutically acceptable capsules such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect and the spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels (co..1, lines 40-54). Sherman's formulation comprises an extended release formulation of venlafaxine hydrochloride is in the form of spheroids comprising a therapeutically effective amount of venlafaxine hydrochloride, microcrystalline cellulose and optionally hydroxypropylmethyl cellulose coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose (col.2, line 65 to col.3, line 5). Sherman teaches that his extended release formulation compromise about 6-40% venlafaxine, preferably between 30-40% and optionally from about 0.225% to 1% by weight of hydroxypropylmethyl

cellulose (col.3, lines 10 and line 20-25). Sherman additionally teaches that his drug is film coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about 2-12% on the wt/wt basis of the final product (col.4, lines 13-17). Sherman teaches that other equivalents of the hydroxypropylmethyl cellulose and ethyl cellulose having the same physical and chemical characteristics may be substituted in his formulation (col.4, line 44-47). Sherman also teaches the use of binders such as polyvinylpyrrolidone in his formulation (col.5, 4-5).

Sherman does not teach the controlled release formulation of Venlafaxine hydrochloride in the form of mini-tablets, and the coating composition comprising the polymer and the water-soluble component as described in instant claims 6-17.

Oosterbaan teaches low water soluble salts of venlafaxine in a variety of dosage forms including hydrogel-based extended release dosage forms (abstract). Oosterbaan teaches oral dosage forms of venlafaxine maleate which includes tablets, capsules, powders etc. including hard gelatin capsules that can be filled with powder, pellets, granules, small tablets or mini tablets and he capsule or the material place within can be coated for enteric or modified release (col.7, lines 29-42). Oosterbaan teaches that the most desired dosage form is the extended release dosage form (col.7, lines 47-48). Oosterbaan teaches that pharmaceutically acceptable excipients are well known in the art and include diluents, fillers, binders, lubricants, disintegrants, glidants, colorants, pigments, taste masking agents, sweeteners, plasticizers, and any acceptable auxiliary substances such as absorption enhancers, penetration enhancers, surfactants, co-

surfactants, and specialized oils. The proper excipient(s) are selected based in part on the dosage form, the intended mode of administration, the intended release rate, and manufacturing reliability (col.6, lines 50-59). Oosterbaan teaches hydrophilic matrix material in extended release matrix tablet to comprising a polymeric material that swells upon contact with water and exemplifies hydroxypropylmethylcellulose (HPMC) among others (col.8, lines 50-54) and additionally teaches inert matrix material which provides a tortuous path for the drug to escape the dosage form thereby controlling diffusion of the drug and exemplifies ethylcellulose (ETHOCEL) (col.8, lines 61-64). Oosterbaan teaches that the hydrogel tablet of his invention comprises 10-50% of venlafaxine maleate and 30-75% of the hydrogel-forming agent, preferably an HPMC (hydroxypropylmethyl cellulose) and the composition may further comprised other inert ingredients such as fillers, lubricants etc (col. 9, lines 21-35) Oosterbaan also teaches the tablets to be prepared according to any standard tabletting technique, e.g. wet granulation, dry granulation or direct compression (col.9, lines 37-41). Oosterbaan further teaches the mini-tablets to be one of the preferred embodiments of his invention which have a diameter of 1-3 mm and one or more of the tablets preferably loaded into a single capsule to provide a unit dose. Oosterbaan teaches that the small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile which is not as easily obtained with a proportionally larger hydrogel tablet (col.9, lines 52-59 and 65). Oosterbaan teaches the release to be a function of the volume to surface area ratio, and accordingly scaling up the amount and size of a satisfactory 37.5 mg tablet to 150 mg tablet will likely not result in a satisfactory release

profile, because the volume to surface area ratio is different between the two tablets. As a consequence of which for each desired single dosage level, a separate formulation, size and/or shape would be needed. However by using small or mini tablets in a single capsule, only one tablet formulation and shape is needed to produce multiple dosage strengths and typically a small or mini-tablet containing 5 to 50 mg of venlafaxine maleate .Depending on the size of the tablet and the capsule, from 1 to 10 or more small or mini-tablets can be placed in the capsule (col 9, line 66 to col.10 line 14). Oosterbaan additionally teaches that in addition to filling capsules with small or mini-tablets, an extended release capsule can be formed by filling it with more traditional pellets, beads, and/or spheres.

Mulye teaches coating composition for coating a solid dosage form of the medicament directed to a system for the controlled release formulation (abstract). Mulye's coating formulation can be used to coat various cores that contain tablets, spheroids, micro spheres, seeds, pellets, or other multi-particulate systems to achieve a controlled release of the main ingredient longer than 24 hours [0040]. Muyle also teaches that the first component of the coating is the water insoluble polymer ([0045], lines 1-2) and lists Eudragit RS ® and Eudragit RL® [0048] as suitable choices. Mulye teaches that the insoluble polymer more preferably comprises at least 60% by dry weight of the coating material [0052]. Mulye further states that the second component of the coating is a water soluble compound ([0054], lines 1-2) such as lactose or sucrose, propylene glycol, sugar alcohols, polydextrose etc. [0055] and preferably makes up 20-30% of the coating [0060] . In examples 1, 2 and 5, Mulye teaches the polymer: water

soluble component ratio used in the coating process to be 4:1, 3: 1 and 9:1 respectively [0012] - [0117] reference claims 2 and 9-10). According to Mulye, the amount of coating applied is sufficient to retard the release of the active component at a desired rate, therefore the coating composition is applied to the core in a thickness sufficient to obtain the desired release profile of a therapeutically active agent when the coated substrate is exposed to aqueous solutions and Mulye prefers the coating composition of his invention to be applied to the core at a thickness ranging from about 1% to about 15% by dry weight of the composition more preferably from about 3 to about 6% of the composition ([0089], reference claims 24--26). Mulye additionally teaches the coating compositions to comprise of other additives normally found in coatings used in the pharmaceutical arts such as plasticizers ([0066] and reference claim 14), wetting agents, lubricants, coloring agents [0065], masking agents and the like [0063]. Mulye also teaches the method of preparation of the coating which is by art recognized techniques which includes dispersion of the polymer and the water soluble compound in pharmaceutically acceptable solvent such as water [0068]. Muyle teaches the coating composition of his invention is coated onto the core containing a drug in any conventional oral unit dosage form, such as a tablet, capsule, pill, granule or powder to form the desired preparation where in the coating composition coats the central core element utilizing conventional methods known in the art such as using a fluidized bed or pan; spraying or painting the suspension of the composition onto the formulation; or using a fluid bed bottom spray coater [0083]. Muyle teaches that the coating forms films around the core and the strength of the film is dependent on the presence of water

insoluble polymer and the water soluble component [0091]. Finally Muyle teaches advantages to using his coating compositions to coat controlled release formulation as follows: (1) it is completely aqueous; there is an avoidance of organic solvents, which have inherent safety concerns, inflammability, carcinogenicity, environmental concerns costs, safety in general. It is also very simple to make. (2)The uniformly dispersed component allows uniform wetting of the coat, it yields better uniformity of dry release between tablet and allows for better adhesion to the water wettable core (3) The coat is wettable. (4) The rate of release can be controlled by controlling the porosity of the coat or the thickness of the coat ([0093]-[0099]). Muyle teaches sustained release formulations comprising any one of the active ingredients at concentrations of 0.5-90% [0070-0071] comprising fillers such as lactose preferably at 30-40% [0073], binders which helps promote adhesion of the drug to the beads preferably at concentrations of 3-15% exemplified by polyvinylpyrrolidone [0077-0078] and sellable polymers such as hydroxypropylmethylcellulose at concentrations of 2-20% wt based on the weight of the core [0081-0082]

With regards to instant claims 2 and 5 which recites the use of a conjugation agent. Binding agents taught by Sherman and Muyle such as polyvinylpyrrolidone reads on the conjugation agent. Conjugation agent is recited in the instant disclosure as an agent which forms a bond between the swellable and non-swellable polymer and could be surfactant or a polymer and examples of the polymer include 'polyvinylpyrrolidone' (instant disclosure, page 5, section iv). As such polyvinylpyrrolidone taught as binding agent by both Sherman and Muyle reads on this limitation. As suggested by the

applicant in the disclosure, surfactants such as sodium lauryl sulphate and the polymer such as poly vinylpyrrolidone with reference to controlled release formulation are functional equivalents and both provide binding of the swellable and non-swellable polymers. As such use of such a binder in the pharmaceutical arts for the formulation of controlled release dosage forms is well known and an ordinary skilled artisan would have been motivated to use a binding agent as taught by Sherman and Muyle in the development of a venlafaxine hydrochloride tablet.

With regards to the instant claim 22, which recites the limitation that the mini-tablets are partially or totally coated by a coating layer or coating film that is functional only during the first 2-4 hours of the drug release, as taught by Muyle, who incidentally explicitly teaches a coating composition identical to that which is instantly claimed with a polymer and a water-soluble component, the release rate of the drug can be controlled by varying the thickness of the coating on the mini-tablets. Muyle provides motivation to one of ordinary skill in the art to utilize the coating composition of his invention since it provides the advantage of uniform thickness and by varying the thickness of the coatings the drug release rate can be altered and it would be obvious to one of ordinary skill in the art to test formulations with varying coating thickness to arrive at the instantly claimed release rate.

With regards to instant claim 20, which recites the limitation where in the linearity between the total weight of the mini-tablets and the strength of the said dosage form is achieved. One of ordinary skill in the art can easily conceive a controlled release tablet with such a feature given the teachings of Oosterbaan. Oosterbaan teaches that the

small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile which is not as easily obtained with a proportionally larger hydrogel tablet and by using small or mini tablets in a single capsule, only one tablet formulation and shape is needed to produce multiple dosage strengths and typically a small or mini-tablet containing 5 to 50 mg of venlafaxine maleate .As such one of ordinary skill in the art can easily envisage dosage forms of multiple strengths each comprising a different number of mini-tablets within a capsule thereby achieving a clear linear relationship between the total weight of the mini-tablets with the strength of the said dosage form.

In view of the foregoing references, the instantly claimed pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCl, in the form of mini-tablets would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Sherman teaches extended release formulations comprising Venlafaxine hydrochloride in the form of coated spherules which are placed in pharmaceutically acceptable capsules. Oosterbaan teaches sustained release Venlafaxine maleate dosage forms in the form of mini-tablets which are encapsulated in an ingle capsule. Oosterbaan provides one of ordinary skill in the art motivation to develop a mini-tablet formulation method of his invention using Venlafaxine hydrochloride taught by Sherman by this teachings that by developing the extended release formulation in the mini tablet form one would be able to provide multiple dosage strengths of the drug by varying the number of tablets that is encapsulated. As such only a single tablet formulation is needed to produce multiple

dosage strengths. An ordinarily skilled artisan would be imbued with a reasonable expectation of success that a mini-tablet formulation of venlafaxine hydrochloride would provide flexibility in terms of multiple dosage strength formulation without necessarily modifying the release profile of the drug.

In view of the foregoing references, the instantly claimed pharmaceutical dosage form comprising an extended release formulation of the water-soluble drug substance Venlafaxine HCL in the form of hard gelatin capsule containing coated mini-tablets would have also been prima facia obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Muyle in combination with Sherman and Oosterbaan. Controlled release dosage form is a well established art in pharmaceutical sciences and the various excipients such as gelling agents, non-swelling polymer, conjugation agent and coating formulations comprising a polymer and a water soluble component were known in the art at the time of the invention Delivery of Venlafaxine hydrochloride in the controlled release form is well established as taught by Sherman. Use of Mini-tablets in a capsule as one of the controlled release dosage form was well known at the time of the invention as evidenced by Oosterbaan. An ordinarily skilled artisan would therefore be motivated to substitute the spherule form of controlled release Venlafaxine hydrochloride dosage form taught by Sherman with the mini-tablet form taught by Oosterbaan given the advantages of being able to deliver multiple strength dosages by preparing just one form of the drug. Coating of tablets in pharmaceutical sciences to establish controlled delivery of the drug is also well established art in pharmaceutical sciences. Muyle provides one of ordinary skill in the

art motivation to utilize his method of coating tablets to achieve controlled release as it offers several advantages over other methods such as increased safety, reduced costs, uniformity of coating which provides improved adhesion, ability to control the release by varying the thickness etc. As such one of ordinary skill in the art would be motivated to utilize the more advantageous method of coating tablets as taught by Muyle to coat venlafaxine hydrochloride mini-tablets formulated by combining the teachings of Sherman and Oosterbaan. The advantages of such a coating procedure as recited by Muyle would provide an ordinary skilled artisan a reasonable expectation of success that such a coating would provide for a better formulated dosage form with a well controlled release of the active drug.

Conclusion

Claims 1-23 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
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